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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	**PAPER NUMBER**
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/715,417	STRATEN ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/12/08*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,12,13,18,19,21,23-25,28-31,33-36 and 38-50* is/are pending in the application.

4a) Of the above claim(s) *12,13,18,19,29-31 and 41-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,21,23-25,28,33-36,38-40 and 50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/12/08 has been entered.

Applicant's amendment filed 12/12/08 is acknowledged and has been entered.

2. Applicant is reminded of Applicant's election with traverse of Group I and species of SEQ ID NO: 14 as the native human survivin peptide sequence and SEQ ID NO: 36 as the modified survivin peptide in Applicant's response filed 12/21/06. The Examiner notes that the instant claims no longer recite either SEQ ID NO.

Claims 1, 21, 23-25, 28, 33-36, 38-40 and 50 are currently being examined.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 21, 23-25, 28, 33-36, 38-40 and 50 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the claimed invention, an MHC Class I-restricted epitope peptide derived from survivin, comprising the epitope peptide of SEQ ID NO: 5, wherein the epitope peptide is capable of eliciting INF-γ producing cells (including at the level recited in base claim 21) in a PBL population of a patient having cancer disease wherein survivin is expressed (including those diseases recited in dependent claims 23 and 24), a composition or a pharmaceutical composition or vaccine composition comprising said peptide, a complex of an HLA molecule or fragment thereof and the said peptide in

monomeric or multimeric form, and including all other limitations of ultimate base claim 1. In addition claim 28 recites that the pharmaceutical composition comprising the peptide is an immunogenic composition capable of eliciting an immune response against a cancer disease, *i.e.,* is capable of treating cancer. The claims that recite vaccine encompass a peptide that is capable of prophylaxis (claims 33-35 and 50).

The instant claims encompass an MHC class I-restricted epitope peptide, composition, pharmaceutical composition, and vaccine that is or comprises an MHC class I restricted epitope peptide *derived* from survivin *comprising* the epitope peptide *of* SEQ ID NO: 5, *i.e.,* the "epitope peptide derived from survivin" may be a subsequence of SEQ ID NO: 5 and comprise undisclosed N- and/or-C terminal flanking sequence that is not necessarily contiguous flanking sequence of the protein of origin. As such, the instant claims are drawn to a peptide of partially disclosed structure, or a composition or complex comprising said peptide. There is insufficient disclosure in the specification on such a peptide, composition, vaccine, and complex thereof.

The specification does not disclose a representative number of species of MHC Class I-restricted epitope peptide as claimed, the peptide consisting of SEQ ID NO: 5 being the only species so disclosed, whereas the claims encompass a peptide that may comprise SEQ ID NO: 5 or a subsequence of SEQ ID NO: 5 with undisclosed flanking sequences not necessarily from the protein of origin, or composition, vaccine or complex thereof. The claims encompass a peptide that may be any MHC Class I-restricted epitope peptide, not just HLA-A2.1 that binds SEQ ID NO: 5. It was well known in the art at the time of invention that hundreds of Class I molecules exist. Even though the functional limitation "wherein the epitope peptide is capable of eliciting INF-γ producing cells in a PBL population of a patient having cancer disease wherein survivin is expressed" in recited in ultimate base claim 1, disclosure of the correlation between the flanking sequences, binding to any MHC Class I molecule and producing the claimed functional limitation is not present.

The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.,* structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the Applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Fri. January 5, 2001, see especially page 1106 column 3). In The Regents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412) 19 F. 3d 1559, the court noted: "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06

(discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." The court has further stated that "Adequate written description requires a precise definition, such as by structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention." Id. at 1566, 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). Also see Enzo-Biochem v. Gen-Probe 01-1230 (CAFC 2002).

The specification discloses that "survivin is a recently identified member of the family of inhibitors of apoptosis proteins (IAPs)" ([0009]), and that "U.S. Pat. No. 6,245,523 discloses the isolation of purified survivin and it provides nucleic acid molecules that encode the survivin protein, and antibodies and other molecules that bind to survivin U.S. Pat. No. 6,245,523 also discloses anti-apoptotically active fragments of the survivin protein and variants hereof wherein an amino acid residue has been inserted N- or C-terminal to, or within, the disclosed survivin sequence. It is specifically disclosed that such peptides should contain key functional residues required for apoptosis, *i.e.,* Trp at position 67, Pro at position 73 and Cys at position 84" ([0011]). The specification discloses that "survivin is a recently identified member of the family of inhibitors of apoptosis proteins (IAPs). In a global gene expression analysis of about 4 million transcripts, survivin was identified as one of the top genes invariably up-regulated in many types of cancer but not in normal tissue (8)" [0009].

The specification further discloses that the peptides of the invention are derived from the known sequence of survivin, *e.g.,* the sequence disclosed in U.S. Pat. No. 6,245,523, and that the selection of peptides potentially having the ability to bind to a particular HLA molecule can be made by the alignment of known sequences that bind to a given particular HLA molecule to thereby reveal the predominance of a few related amino acids at particular positions in the peptides, *i.e.,* anchor residues ([0027]). The specification discloses "a simple approach to identifying peptides of the invention includes the following steps: selecting a particular HLA molecule, e.g. one occurring at a high rate in a given population, carrying out an alignment analysis as described above to identify "anchor residue motifs" in the survivin protein, isolating or constructing peptides of a suitable size that comprise one or more of the identified anchor residues and testing the resulting peptides for (i) capability to bind to the particular HLA molecule using the assembly assay as described herein, (ii) the capability of the peptides to elicit INF-.gamma.-producing cells in a PBL population of a cancer patient at a frequency of

at least 1 per 10.sup.4 PBLs as determined by an ELISPOT assay as described herein, and/or (iii) the capability of the peptides to detect *in situ* in a tumour tissue CTLs that are reactive with the epitope peptides being tested" ([0031]).

The specification discloses that some nonamer and decamer peptides that are subsequences of human survivin or substitution variants of said peptides can bind to selected HLA class I molecules (especially Table 4). The specification discloses that five stage IV melanoma patients were vaccinated with the modified HLA-A2 restricted sur1M2 peptide (SEQ ID NO: 5) loaded onto autologous dendritic cells, resulting in a strong T cell response to said peptide, and the detection of infiltration of survivin reactive cells into visceral and soft tissue metastases using *in situ* peptide/HLA-A2 multimer staining (page 44 at lines 4-11). The specification discloses that SEQ ID NO; 1, 4 and 5 bind to HLA-A2 with *C50* of 30, 1 and 1 uM, respectively, and that CTL or TIL from some CLL or melanoma patients could recognize or cross-react with complexes of SEQ ID NO: 5 and HLA-A2 (especially Table 1). The specification discloses injection of dendritic cell loaded SEQ ID NO: 5, 10 or 3 into cancer patients, and demonstration of induction of HLA-A2/SEQ ID NO: 10-specific T cells with the capacity to home to soft tissue and visceral metastases (especially pages 44-48), but does not disclose the relevance of the treatment with the clinical outcome observed, *i.e.,* how the composition or vaccine comprising the peptides treat or prevent cancer.

The specification does not disclose the identity of the amino acid residues that flank the recited SEQ ID NO that would allow the peptide comprising the recited SEQ ID NO to bind to one of hundreds of undisclosed MHC Class I molecule or be processed to a peptide that could bind, or to a peptide that can treat cancer or act as a prophylactic (vaccine), nor which subsequence of SEQ ID NO: 5 in combination with the undisclosed flanking sequence, would confer the claimed functional properties.

Given these considerations, adequate written description has not been established.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's arguments are of record in the amendment filed 12/12/08 on pages 9-11, briefly that Applicant has amended claims 1 and 20 to direct the claims to subject matter corresponding to SEQ ID NO: 5 (the Sur1M2 peptide), the specification describes clinical benefits in all patients receiving full treatment, and that this treatment is accompanied by a highly specific T-cell response to the Sur1M2 peptide presented in the vaccine. In addition, Applicant presents arguments to the therapeutic benefits pertaining to use of SEQ IDNO: 5 and the specificity of the T cell response thereto.

Claim 20 has been cancelled by the said amendment. Although claim 1 has been amended, the claim encompasses broader subject matter than a peptide consisting of SEQ ID NO: 5, as enunciated supra. With regard to Applicant's remaining arguments as to therapeutic benefit and specificity of T cell response, these arguments are directed to enablement issues. None-the-less, to address these arguments, the specification discloses that the peptide is not administered by itself, but rather when loaded onto autologous dendritic cells, *i.e.,* the composition is a dendritic cell composition, not an isolated peptide composition as is recited in the instant claims. Dendritic cell compositions comprise numerous additional components that may aid in eliciting an immune response. Claims 25, 28, 33-35 and 50 are drawn to a pharmaceutical composition or vaccine composition comprising the epitope peptide recited in base claim 1.

5. Claims 1, 21, 23-25, 28, 33-36, 38-40 and 50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO: 5, composition thereof, or HLA-A2/complex or multimer complex thereof, does not reasonably provide enablement for an MHC Class I-restricted epitope peptide derived from survivin comprising the epitope peptide of SEQ ID NO: 5, wherein the epitope peptide is capable of eliciting INF-γ producing cells (including at the level recited in base claim 21) in a PBL population of a patient having cancer disease wherein survivin is expressed (including those diseases recited in dependent claims 23 and 24), a composition or a pharmaceutical composition or vaccine composition comprising said peptide, a complex of an HLA molecule or fragment thereof and the said peptide in monomeric or multimeric form, and including all other limitations of ultimate base claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification has not enabled the breadth of the claimed invention because the claims encompass an MHC class I-restricted epitope peptide, composition, pharmaceutical composition, and vaccine that is or comprises an MHC class I restricted epitope peptide *derived* from survivin *comprising* the epitope peptide *of* SEQ ID NO: 5*, i.e.,* the "epitope peptide derived from survivin" may be a subsequence of SEQ ID NO: 5 and comprise undisclosed N- and/or-C terminal flanking sequence that is not necessarily contiguous flanking sequence of the protein of origin. As such, the instant claims are drawn to a peptide of partially disclosed structure, or a composition or complex comprising said peptide. In addition claim 28 recites that the pharmaceutical composition comprising the peptide is an immunogenic composition capable of eliciting an immune response against a cancer disease, *i.e.,* is capable of treating cancer. The claims that recite vaccine encompass a peptide that is capable of prophylaxis.

The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed invention can be made and/or used.

The specification discloses that "survivin is a recently identified member of the family of inhibitors of apoptosis proteins (IAPs)" ([0009]), and that "U.S. Pat. No. 6,245,523 discloses the isolation of purified survivin and it provides nucleic acid molecules that encode the survivin protein, and antibodies and other molecules that bind to survivin U.S. Pat. No. 6,245,523 also discloses anti-apoptotically active fragments of the survivin protein and variants hereof wherein an amino acid residue has been inserted N- or C-terminal to, or within, the disclosed survivin sequence. It is specifically disclosed that such peptides should contain key functional residues required for apoptosis, *i.e.,* Trp at position 67, Pro at position 73 and Cys at position 84" ([0011]). The specification discloses that "survivin is a recently identified member of the family of inhibitors of apoptosis proteins (IAPs). In a global gene expression analysis of about 4 million transcripts, survivin was identified as one of the top genes invariably up-regulated in many types of cancer but not in normal tissue (8)" [0009].

The specification further discloses that the peptides of the invention are derived from the known sequence of survivin, *e.g.,* the sequence disclosed in U.S. Pat. No. 6,245,523, and that the selection of peptides potentially having the ability to bind to a particular HLA molecule can be made by the alignment of known sequences that bind to a given particular HLA molecule to thereby reveal the predominance of a few related amino acids at particular positions in the peptides, *i.e.,* anchor residues ([0027]). The specification discloses "a simple approach to identifying peptides of the invention includes the following steps: selecting a particular HLA molecule, e.g. one occurring at a high rate in a given population, carrying out an alignment analysis as described above to identify "anchor residue motifs" in the survivin protein, isolating or constructing peptides of a suitable size that comprise one or more of the identified anchor residues and testing the resulting peptides for (i) capability to bind to the particular HLA molecule using the assembly assay as described herein, (ii) the capability of the peptides to elicit INF-.gamma.-producing cells in a PBL population of a cancer patient at a frequency of at least 1 per 10.sup.4 PBLs as determined by an ELISPOT assay as described herein, and/or (iii) the capability of the peptides to detect *in situ* in a tumour tissue CTLs that are reactive with the epitope peptides being tested" ([0031]).

Celis *et al* (Mol. Immunol. 1994. 31(18): 1423-1430, of record) teach that in order to establish whether a peptide is immunogenic said peptide needs to be tested in assays that actually establish that a peptide is immunogenic. Celis *et al* teach that "In addition to MHC binding, other factors such as antigen processing, peptide transport and the composition of the T-cell receptor repertoire could determine whether any of these peptides can function as effective CTL antigens. Ochoa-Garay *et al* (Mol. Immunol. 1997. 34(1): 273-281) teach that "In summary, the results in this report indicate that the immunogenicity of a peptide cannot always be predicted from its affinity for class I or the presence of class I binding motifs. In addition, our data show that variables such as CTL precursor frequency, peptide hydrophobicity and stability can influence the *in vitro* induction of CTL responses" (especially page 279, last sentence and continuing onto

page 280). Karin *et al* teach that a single substitution in an amino acid, wherein said amino acid plays no role in MHC binding can completely abrogate the immunogenicity of an otherwise immunogenic peptide (especially Summary and Table 1).

In addition, the art recognizes that for a peptide to be a T cell epitope, the length of the peptide is important for binding to HLA (along with the presence of anchor (or "motif") amino acid residues present within the peptide). The peptides that bind to class I molecules have a predominant length, *i.e.,* a minimum of 8 or 9 amino acid residues for a class I MHC restricted T cell epitope peptide. A primary factor for this is that amino acid residues at the amino- and carboxy-termini of peptides binding to class I molecules interact with conserved amino acid residues in pockets ("A","F") located at opposite ends of the binding groove of the class I molecule, giving rise to a common orientation of the peptides in the binding site (Engelhard at page 14, column 1, lines 16-27, Curr. Opin. Biol. 1994, 6: 13-23, of record) Thus, the amino acid residues at the peptides' termini make a network of hydrogen bonds with conserved residues on the sides and bottom of the peptide binding groove of class I molecules. These interactions are important for holding the peptides in the binding groove and for stabilizing the complex (Guo *et al* at page 366, column 1 lines 1-10, Nature 1992, 360: 364-366, of record) "...the preferred length (of the peptide) is determined by the minimum amount of peptide required to span the center of the binding site and optimize the interactions at the ends", but that the predominant length is 9 amino acid residues (Engelhard at page 14, column 1, lines 23-27, of record).

The specification discloses that some nonamer and decamer peptides that are subsequences of human survivin or substitution variants of said peptides can bind to selected HLA class I molecules (especially Table 4). The specification discloses that five stage IV melanoma patients were vaccinated with the modified HLA-A2 restricted sur1M2 peptide (SEQ ID NO: 5) loaded onto autologous dendritic cells, resulting in a strong T cell response to said peptide, and the detection of infiltration of survivin reactive cells into visceral and soft tissue metastases using *in situ* peptide/HLA-A2 multimer staining (page 44 at lines 4-11). The specification discloses that SEQ ID NO; 1, 4 and 5 bind to HLA-A2 with *C50* of 30, 1 and 1 uM, respectively, and that CTL or TIL from some CLL or melanoma patients could recognize or cross-react with complexes of SEQ ID NO: 5 and HLA-A2 (especially Table 1). The specification discloses injection of dendritic cell loaded SEQ ID NO: 5, 10 or 3 into cancer patients, and demonstration of induction of HLA-A2/SEQ ID NO: 10-specific T cells with the capacity to home to soft tissue and visceral metastases (especially pages 44-48), but does not disclose the relevance of the treatment with the clinical outcome observed, *i.e.,* how the composition or vaccine comprising the peptides treat or prevent cancer.

Evidentiary reference Matthias Grube *et al* (Blood. 2005, 106(11), part 2, pp 369B, abstract 3, 5145, of record) teach that survivin peptide specific CTL could be detected in individuals with multiple myeloma, and those same CTL were detected in 5% of healthy individuals.

Evidentiary reference Celis (J. Clin. Invest. 2002, 110(12: 1765-1768, of record) teaches that "Unfortunately, the advantages that peptide vaccines have to offer are to some extent diminished by their inherent lack of immunogenicity, which so far has been reflected by their not-so-spectacular results in the clinic. Because the immune system in most species has evolved through time to fight life threatening infectious agents (and perhaps tumors), it should not be surprising that vaccines consisting of aseptic, endotoxin-free peptides are likely to be ignored and will likely be ineffective at inducing T cell immunity. In addition, peptides that are injected in aqueous solutions will be unsuccessful at stimulating CTL responses, either because of their rapid biodegradation (*e.g.,* by proteases) or, worse, because of the induction of T cell tolerance/anergy, which results from the antigenic stimulation of CTLs by non-professional APCs." Celis further teaches that an additional complication resulting from the use of synthetic peptide-derived vaccines is the induction of low affinity CTLs, that while capable of killing target cells that are exogenously pulsed with peptide, are not able to recognize the target cells that naturally process and present the peptide epitope, such as malignant cells. These low quality CTLs would have little effect in fighting and controlling disease (especially page 1765 through the paragraph spanning pages 1765-1766.

Evidentiary reference Marchand *et al* (Exp. Opin. Biol. Therapy. 1(3): 497-510, 2001, of record) teach "It is fair to say that in patients vaccinated with defined antigen, the immune responses induced have been so far very poor, if present. In some studies, immune responses were reported for some patients but without any correlation with the clinical responses. In addition, some patients with complete and long-term regressions of several melanoma metastases failed to mount a detectable response against the antigen present in the vaccine." (last paragraph at column 2 on page 505).

Evidentiary reference Morel *et al* (Immunity 12: 107-117, 2000, of record) teach the treatment of target cells for at least one week with IFN-γ to induce immunoproteasome expression in said target cells, and further teach that a number of antigenic peptides that are efficiently produced by the standard proteasome are not produced by the immunoproteasome. Morel *et al* further teach that a major difference between the two forms of proteasomes in terms of catalytic activity is the severely reduced ability of the immunoproteasome to cleave after acidic residues and also after residues with branched side chains, such as valine (paragraph spanning pages 113-114). Morel *et al* teach that an IFN-γ rich environment such as that found in a lymph node or a tumor mass heavily infiltrated with T cells could cause a proteasome switch in the tumor cells

resulting in a lack of presentation of certain tumor antigens and escape from CTL attack (especially first sentence of the third full paragraph at column 1 on page 114).

Evidentiary reference Andersen *et al* (Cancer Res. 2000, 61: 869-872, IDS reference) teach that they have demonstrated the existence of T cell responses against two survivin deduced epitopes in cancer patients, and "However, at this time we do not know whether *survivin* peptides are actually presented by the tumor cells *in vivo*, because the formal proof for this notion is still lacking" (last paragraph of article).

Evidentiary reference Andersen *et al* (Cancer Res. 2001, 61: 5964-5968, IDS reference) teach that "The ELISPOT methodology represents a strong tool to monitor peptide-specific T-cell response. However, although it has been shown that ELISPOT reactivity in most cases correlates with the capacity to lyse the target cell, the formal proof for this notion can be given only directly" (page 5966 at column 2, lines 3-7).

The disclosed use of a pharmaceutical composition of the invention is to treat cancer ([0022]).

Evidentiary reference Reker *et al* (Cancer Biol. & Therapy. 2004, 3(2): 173-179, of record) teach "To date, it is not known whether survivin is indeed a tumor rejection antigen, *i.e.,* a tumor-associated antigen that can elicit immune responses in patients, which significantly impacts tumor growth…Thus if efficient immunity can be successfully elicited in cancer patients, without the induction of severe autoimmunity, survivin clearly becomes a prime candidate for a widely applicable cancer vaccine" (last paragraph of article).

Evidentiary reference Boon *et al* (Ann. Rev. Immunol. 2006, 24: 175-208) teach "Therapeutic vaccination of metastatic melanoma patients with these antigens [*i.e.,* melanoma antigens] is followed by tumor regressions in only a small minority of the patients (page 175, abstract). Boon *et al* further teach "In conclusion, therapeutic success following vaccination may not depend on the number of T cells produced directly by the vaccine, but rather on the production of a T cell clone with functional properties that enable it to migrate to the tumor and resist the local immunosuppressive environment long enough to initiate a regression process…To achieve therapeutic success, investigators will probably need to understand the cause of the local immunosuppression in the tumors and find counteracting agents. As stated above, the list of possible immunosuppressive agents present in tumors is considerable. But it will be important to find whether, for each type of tumor, there is a prevalent immunosuppressive agent. Just as many types of tumors have preferred oncogenic pathways that differ from one type of tumor to another, each type of tumor may also have preferred immunosuppressive processes that we must identify to achieve therapeutic success…**Therapeutic vaccination of cancer has not yet proved to be effective enough to become a generally applied cancer treatment**…We do not

believe that melanoma patients suffer from a degree of general immunosuppression, which we believe is restricted to very late-stage patients who are not included in most studies…Therefore, the difference in the quality of the response would be due to a chance event determining, for instance, the functional properties of the unique or the few responder T cell clones elicited by the vaccine. In that case, it will be essential to understand what this crucial functional property is. At the other extreme, the antivaccine T cell responses would be similar in all patients, but the level of resistance of the tumors would vary considerably. In that case investigators would need to identify the main component of this resistance and find ways to counteract it." (especially pages 193-194.

The specification does not disclose any peptide or composition thereof used prophylactically as a vaccine.

Evidentiary reference the Merck Manual (of record) teaches that a vaccine is a suspension of whole or fractionated bacteria or viruses that have been rendered nonpathogenic and is given to induce an immune response and prevent subsequent disease.

Evidentiary reference Encyclopedia Brittanica Online (of record) defines vaccine as a suspension of weakened, killed, or fragmented microorganisms or toxins or of antibodies or lymphocytes that is administered primarily to prevent disease.

The art recognizes that in order to be used for generating an immunogenic response, *i.e.,* for it to be an epitope, and also hence by extension to be used for *ex vivo* or *in situ* diagnosis of survivin reactive T cells of a cancer patient, that the said peptide must bind MHC and also present an epitope recognized by T cells.

Even if there were factual evidence that patients with melanoma or any other cancer or pathological condition could produce a peptide-specific immune response to the claimed peptide in a pharmaceutical composition, there is no factual evidence that the patient's condition would clinically improve, *i.e.,* be 'treated', nor that a vaccine comprising the peptide could prevent a cancer. Based upon the teachings of the evidentiary references cited herein, it is evident that eliciting an immune response is not sufficient to evoke a clinically significant or specific anti-tumor effect.

Therefore, because of the demonstrated unpredictability in the art of cancer immunotherapy and in the absence of sufficient exemplification and guidance, one skilled in the art cannot make and/or use the claimed invention with a reasonable expectation of success. Undue experimentation would be required of one skilled in the art to practice the instant invention. See *In re Wands* 8 USPQ2d 1400 (CAFC 1988).

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's arguments are of record in the amendment filed 12/12/08 on pages 12-17, briefly that: the Examiner's position appears to be that the specification enables peptides, HLA-A2 complexes or multimers, but not vaccines and pharmaceutical compositions, the Examiner appears to require completed human clinical trials to satisfy enablement, the MPEP states that "data generated using in vitro assays or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process" so long as the data is reasonable correlated to the asserted utility, the instant application meets this standard because the Example[s] disclose data from multiple in vitro assays that adequately establish therapeutic utility of the claimed Sur1M2 peptide compositions, including immunogenic compositions and vaccines. Applicant further argues that support for the enablement of the claims is found in the Sorensen *et al* manuscript that has been accepted for publication (Appendix B), that the Examiner appears to cite Matthias *et al* as evidence that the induced Sur1M2 specific CTL response in Example 5 results from dendritic calls alone in the vaccine. Applicant cites recently published Matthias II (Appendix A) for frequency of survivin-specific T cells and Titzer *et al* (Appendix C) for proof of concept of vaccination therapy using peptide-pulsed dendritic cells.

However, the claims are not drawn to SEQ ID NO: 5, but rather to an MHC Class I-restricted epitope peptide that comprises either SEQ ID NO: 5 or a subsequence of SEQ ID NO: 5, either one of which may comprise undisclosed flanking sequence not found in the protein of origin, wherein the MHC Class I to which it binds is not limited among the hundreds known in the art to exist at the time the invention was made. Therefore, the breadth of the claims is larger than that of the Sur1M2 peptide exemplified in the instant specification. The evidentiary references teach unpredictability in the art of predicting T cell epitope peptides, see for instance Celis *et al*, supra. Neither are the claims drawn to a dendritic cell vaccine or composition, but rather to a peptide. The evidentiary references speak to unpredictability in the art in peptide vaccines or compositions and their inherent lack of immunogenicity by themselves, *i.e.,* see Celis *et al* supra, for example, aseptic, endotoxin-free peptides may be ignored, biodegradation of peptides, induction of T cell tolerance or anergy by peptides, induction of low affinity CTLs by peptides.

There are no working examples of using SEQ ID NO: 5 or a peptide comprising SEQ ID NO: 5 or a subsequence of it to prevent cancer or any other condition.

The Examiner is not requiring completed human clinical trials to satisfy enablement; however, in the absence of a working example of prophylaxis with SEQ ID NO: 5 or a peptide comprising SEQ ID NO: 5, or a peptide comprising a subsequence of SEQ ID NO: 5, derived from survivin, neither the *in vivo* or *in vitro* data disclosed in the instant specification provide a reasonable correlation for prophylactic use. Nor does the specification provide a reasonable correlation for treatment of cancer due to the breadth

of the claims and the fact that the *in vivo* and *in vitro* data are generated not with a peptide composition as in the instant claims, but rather with a dendritic cell composition. Dr. Andersen has made a statement on the record that phase III clinical trials are the only firm proof that a vaccine works. The Examples in the instant specification are also accomplished using dendritic cell compositions.

With regard to Example 1 in the specification that deals with *in vitro* assays measuring binding of SEQ ID NO: 5 to HLA-A2.1 molecules and the reactivity of the resulting complexes with T cells from CLL patients by ELISPOT assay, evidentiary reference Andersen et al (2001) teaches "However, although it has been shown that ELISPOT reactivity in most cases correlates with the capability to lyse the target cell, the formal proof for this notion can be given only directly" as enunciated supra.

Mathias *et al* is not cited by the Examiner as evidence that the induced Sur1M2 specific CTL response in Example 5 of the instant specification results from dendritic cells alone in the vaccine. However, other evidentiary references cited herein have put forth the concept of unpredictability in the art of administering peptides by themselves, *i.e.,* not as part of a dendritic cell composition. And with regard to the Titzer *et al* reference, the instant rejection does not question proof of concept of immunization using peptide-pulsed dendritic cells, but rather treatment or prevention using the peptide alone.

The Mathias *et al* reference in Appendix A used a peptide from survivin (not SEQ ID NO: 5 of the instant application) to detect peptide-specific T cells in 23 patients or 21 healthy volunteers. This reference does not provide enablement for the peptide recited in the instant claims, nor for SEQ ID NO: 5 for treatment or prophylaxis. The Boon *et al* evidentiary reference cited herein speaks to unpredictability in the art of treating a cancer using a peptide, even when that peptide causes stimulation of CTL that can migrate to and infiltrate a tumor.

6. Claim 24 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claim encompass a peptide that is capable of eliciting INF-gamma producing cells in a PBL population of a patient having a cancer disease, said INF-gamma producing cells having cytotoxic effect against survivin expressing cells of a cancer cell line, including a line selected from the group consisting of the breast cancer cell line MCF-7 and the melanoma cell line FM3. There is insufficient disclosure in the specification on such cell lines.

The Examiner notes the US 20040176573 publication of the instant application discloses that MCF-7 is available from ATCC, *i.e.,* "[0127] Conventional [51Cr]-release assays for CTL-mediated cytotoxicity were carried out as described in (13). Target cells were autologous EBV-transformed B-cell lines, the HLA-A2 positive breast cancer cell line MCF-7 (available at ATCC), the HLA-A2 positive melanoma cell line FM3 (38), the HLA-A2 negative breast cancer cell line BT-20 (available from ATCC) and the HLA-A2 negative melanoma cell line FM45 (38). All cancer cell lines expressed survivin as examined by RT-PCR (data not shown)."

It is also noted by the Examiner that Applicant's amendment filed 9/24/07 (on page 24) as well as the said declaration of Dr. Andersen under 37 CFR 1.132 (at item #6 on page 3) states "[t]he cell line was originally described by Kirkin *et al* (Cancer Immunol. Immunother, 41: 71-81, 1995) [the aforementioned reference 38 disclosed at [0127] above] and is well recognized within the art." However, the cell line must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public as enunciated below.

The FM3 cell line is essential to the claimed invention. The reproduction of an identical cell line is an extremely unpredictable event. The cell line must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The instant specification does not disclose a repeatable process to obtain the cell line, and it is not apparent if the cell line is readily available to the public.

If a deposit was made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicants, assignees or a statement by an attorney of record over his or her signature and registration number stating that the deposit has been made under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application is required.

If a deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. 1.801-1.809, an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(A) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(B) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(C) the deposit will be maintained in a public depository for a period of 30 years after the date of deposit or 5 years after the last request for a sample or for the enforceable life of the patent whichever is longer;

(D) a viability statement in accordance with the provisions of 37 C.F.R. 1.807;

(E) the deposit will be replaced should it become necessary due to inviability, contamination, or loss of capability to function in the manner described in the specification.

Furthermore, unless the deposit was made at or before the time of filing, a declaration filed under 37 C.F.R. 1.132 is necessary to construct a chain of custody. Cell line .... was deposited after the time of filing. The declaration, executed by a person in a position to know, should identify the deposited cell line by its depository accession number, establish that the deposited cell line is the same as that described in the specification, and establish that the deposited plasmid was in Applicants possession at the time of filing. In re Lundak, 27 USPQ 90.

Biological materials must be known and readily available to the public (See MPEP 2404.01). Neither concept alone is sufficient. The Office will accept commercial availability as evidence that a biological material is known and readily available only when the evidence is clear and convincing that the public has access to the material. A product could be commercially available but only at a price that effectively eliminates accessibility to those desiring to obtain a sample. The relationship between the applicant relying on a biological material and the commercial supplier is one factor that would be considered in determining whether the biological material was known and readily available. However, the mere fact that the biological material is commercially available only through the patent holder or the patent holder's agents or assigns shall not, by itself, justify a finding that the necessary material is not readily available, absent reason to believe that access to the biological material would later be improperly restricted.

Therefore, because of the unpredictability in the art of making an identical cell line, and by extension a peptide that is capable of eliciting cells that have a cytotoxic effect against said cell lines, one skilled in the art cannot make and/or use the claimed invention with a reasonable expectation of success. Undue experimentation would be required of one skilled in the art to practice the instant invention. See *In re Wands* 8 USPQ2d 1400 (CAFC 1988).

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's said arguments are of record on page 18 of the amendment filed 12/12/08.

Applicant argues that the breast cancer cell line MCF-7 is commercially available from the LGC PROMOchem/ATCC as ATCC number HTB-22TM and provides a hyperlink address.

However, a search of the address brings up a message that the page cannot be found.

Applicant further argues that the melanoma cell line FM3 is commercially available from the ESTDAB database and provides a hyperlink address.

However, a search of the address brings up a message that the file is not found.

A third hyperlink address is cited by Applicant to provide the terms for ordering cells from the said database.

However, the terms explained are "Access to the cells in the cell bank is restricted to bona fide investigators after they have signed Material Transfer Agreements (MTAs) as provided by the original donors of the lines. This service is of nominal cost to the user." Thus, although the cost is not an impediment to commercial availability, it appears that additional restrictions are put on requestors that they must be "bona fide investigators," whatever that phrase includes in the context of the agreement.

7. The attempt to incorporate subject matter (the FM3 melanoma cell line) into this application by reference to Kirkin *et al* (Cancer Immunol. Immunother, 41: 71-81, 1995) at [0127] and [0272] of the US 20040176573 publication of the instant application is ineffective because the incorporation of *essential* material in the specification by reference to an unpublished U.S. application, foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office. The amendment must be accompanied by a statement executed by the Applicant, or a practitioner representing the Applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. 37 CFR 1.57(f).

The attempt to incorporate subject matter into the instant application by reference to a publication is improper because an application as filed must be complete in itself in order to comply with 35 USC 112. An application for a patent when filed may incorporate "essential material" by reference to (1) a US patent or (2) a US patent application publication, which patent or patent publication does not itself incorporate such essential material by reference. "Essential material" is defined as that which is necessary to (1) provide a written description of the claimed invention, and the manner and process of making and using it, in such full, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to make and use the same, and set forth the best mode contemplated by the inventor of carrying out the invention, (2) describe the claimed invention in terms that particularly point out and distinctly claim the invention as required by the second paragraph of 35 USC 112, or (3) describe the structure, material or acts that correspond to a claimed means or step for performing a specified function as required by the sixth paragraph of 35 USC 112. In any application which is to issue as a US patent, essential material may not be incorporated by reference to (1) patents or applications published by foreign countries or a regional patent office, (2) non-patent publications, (3) a US patent or application which itself incorporates "essential material" by reference, or (4) a foreign application. See *In re Fouche*, 439 F.2d 1237, 169 USPQ 429 (CCPA 1971).

Nonessential subject matter may be incorporated by reference to (1) patents or applications published by the US or foreign countries or regional patent offices, (2) prior and concurrently filed, commonly owned US applications, or (3) non-patent publications. Nonessential subject matter is subject matter referred to for purposes of indicating the background of the invention or illustrating the state of the art.

Disclosure made by Applicant in the US 20040176573 publication of the instant specification is as follows:

"[0127] Conventional [51Cr]-release assays for CTL-mediated cytotoxicity were carried out as described in (13). Target cells were autologous EBV-transformed B-cell lines, the HLA-A2 positive breast cancer cell line MCF-7 (available at ATCC), the HLA-A2 positive melanoma cell line FM3 (38), the HLA-A2 negative breast cancer cell line BT-20 (available from ATCC) and the HLA-A2 negative melanoma cell line FM45 (38). All cancer cell lines expressed survivin as examined by RT-PCR (data not shown)", and

"[0272] 38. Kirkin, A. F., Reichert Petersen, T., Olsen, A. C., Li, L., Thor Straten, P., and Zeuthen, J. Generation of human-melanoma specific T lymphocyte clones defining novel cytolytic targets with panels of newly established melanoma cell lines. Cancer Immunol. Immunother., 41: 71-81, 1995."

The Examiner notes that although the words "incorporate" and "by reference" do not appear in the specification in this regard, "the melanoma cell line FM3" is recited in original claim 24, and [0127] discloses reference 38 (Kirkin *et al*) listed in the specification to be associated with FM3.

8. The incorporation by reference will not be effective until correction is made to comply with 37 CFR 1.57(b), (c), or (d). If the incorporated material is relied upon to meet any outstanding objection, rejection, or other requirement imposed by the Office, the correction must be made within any time period set by the Office for responding to the objection, rejection, or other requirement for the incorporation to be effective. Compliance will not be held in abeyance with respect to responding to the objection, rejection, or other requirement for the incorporation to be effective. In no case may the

correction be made later than the close of prosecution as defined in 37 CFR 1.114(b), or abandonment of the application, whichever occurs earlier.

Any correction inserting material by amendment that was previously incorporated by reference must be accompanied by a statement that the material being inserted is the material incorporated by reference and the amendment contains no new matter. 37 CFR 1.57(f).

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1, 21, 23-25, 28, 33-36, 38-40 and 50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

a. Claim 1 is indefinite in the recitation of “epitope peptide” recited at line 3 because it is not clear what is meant, *i.e.,* whether epitope peptide at line three correlates to the first occurrence of the limitation at line 1 that refers to an MHC class I-restricted epitope peptide derived from survivin or the “epitope peptide of SEQ ID NO: 5” that it comprises that is recited at lines 2-3.

b. Claim 24 is indefinite in the recitation of “the breast cancer cell line MCF-7 and the melanoma cell line FM3” because their characteristics are not known. The use of "MCF-7 and FM3" as the sole means of identifying the claimed cell lines renders the claim indefinite because “MCF-7 and FM3" is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designations to define completely distinct cell lines.

Applicant’s arguments have been fully considered, but are not persuasive.

Applicant’s arguments are of record on page 19 of the amendment filed 12/12/08.

Applicant argues that the cell lines are art recognized, and further argues that commercial availability is demonstrated by the three aforementioned hyperlinks.

However, the fact that the cell lines were art recognized and commercial availability are not the issue in the instant rejection. Even if the cell lines are art recognized and commercially available, they are not recited in a fashion that identifies their characteristics, as enunciated above, as using the recited designations as the sole means for identifying the cell lines does not clearly define the claimed products.

c. Claims 33 and 35 both recite the limitation "vaccine" in line 1, and claim 35 also recites “vaccinated” at line 2. There is insufficient antecedent basis for these limitations in the claims.

Claim 35 depends upon claim 33 or claim 34. Claim 34 depends upon claim 33, and claim 33 depends upon claim 28 that recites "an immunogenic composition". Claim 28 depends upon claim 25 that recites "A pharmaceutical composition", and claim 25 depends upon claim 1 that recites "epitope peptide."

11. For the purpose of prior art rejections, the filing date of the instant claims 1, 21, 23-25, 28, 33-36, 38-40 and 50 is deemed to be the filing date of the instant application, *i.e.,* 11/19/03, as neither the parent application serial no. 10/354,090 nor the parent provisional application 60/352,284 support the claimed limitations of the instant application. It is noted by the Examiner, that although SEQ ID NO: 5 is disclosed in the said provisional parent application, and SEQ ID NO: 5 is disclosed in the 10/354,090 parent application, the limitations of claim 1 are not disclosed in either, *i.e.,* “A MHC class I-restricted epitope peptide derived from survivin comprising the epitope peptide of SEQ ID NO: 5.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1, 21, 23, 24, 36 and 38-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Andersen *et al* (Cancer Res. 2/2001, 61: 869-872, IDS reference) as evidenced by Andersen *et al* (Cancer Res. 2001, 61: 5964-5968, IDS reference).

It is noted by the Examiner that the publication date listed on the Andersen *et al* (Cancer Res. 2/2001, 61: 869-872, IDS reference), *i.e.,* 2/2000, is a print error on the part of the publisher. The said reference is published in volume 61, publication date 2/2001.

Andersen *et al* teach the human survivin peptide with the sequence LMLGEFLKL (1 uM, substitution analog peptide), that corresponds to SEQ ID NO: 5 of the instant claims. Andersen *et al* further teach that this peptide has a *C50* (uM) value of 1 uM as determined in an assembly assay for peptide binding to HLA-A2.1 molecules. Andersen *et al* teach that a CLL cancer patient’s IFN-γ producing PBL responded strongly against the analog peptide LMLGEFLKL at 35 per 10^4 cells in an ELISPOT assay (see entire reference, especially Table 1 and Results).

Evidentiary reference Andersen *et al* (2001) teach the human survivin substitution analog peptide LMLGEFLKL (SEQ ID NO: 5 of the instant claims). Andersen *et al* teach that the LMLGEFLKL peptide could be used to isolate and stimulate CTL that produce INF-γ, and that these CTL could lyse (*i.e.,* could exhibit cytotoxicity against the) HLA-A2 positive breast cancer cell line MCF-7 and the HLA-A2-positive melanoma cell line FM3 (see entire reference, especially results).

Claims 38-40 are included in this rejection because the art reference teaches complexes of the survivin HLA-A2-binding peptides with HLA-A2.1, and wherein the HLA/peptide complexes are contacting a T cell, they are multimeric. The instant claims do not recite wherein the complex is isolated.
Claim 36 is included in this rejection because the peptides were used in solution when added to the ELISPOT wells, *i.e.,* were in a composition that was used for *ex vivo* detection or diagnosis of the presence in a cancer patient of survivin reactive T cells among PBL. In addition, the intended use of the composition comprising the peptide "for *ex vivo* or *in situ* diagnosis" recited in the said claims does not carry patentable weight *per se*, and the claims read on the active or essential ingredients of the composition.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's said arguments are of record on pages 20-22 of the amendment filed 12/12/08.

Applicant argues that the earliest priority filing (60/352,284) was filed on January 30, 2002 and includes disclosure of at least SEQ ID NO: 5, to which amended claim 1 is now directed. Applicant presents a table citing instant claim numbers *vs* exemplary support in the said priority filing. Applicant further argues that both Andersen references were published less than one year prior to the filing of Applicant's provisional application 60/352,284, and so the references are not prior art under 35 USC 102(b). Applicant argues that a declaration under 37 CFR 1.132 by Inventor Andersen (of record) with regard to these references has been previously submitted to the Office.

However, the instant claims do not have support in the parent provisional application 60/352,284 because ultimate base claim 1 is not drawn to a peptide consisting of SEQ ID NO: 5 (SEQ ID NO: 5 being disclosed in '284), and the limitations of claim 1 are not supported by the disclosure of '284.

Applicant cites p.3, Table 1, p. 11 at lines 5-18 and p. 12 at lines 15-35 of '284 for support for current claim 1.

p. 3 at Table 1 discloses a peptide consisting of SEQ ID NO: 5, p. 11 at lines 5-18 discloses ELISPOT assay for quantifying peptide epitope-specific IFN-γ releasing

effector cells, and use of Sur1M2 (SEQ ID NO: 5) in the assay, and p. 12 at lines 15-35 disclose survivin-reactive T cells in PBL from HLA-A2 positive breast cancer patients by ELISPOT assay.

In contrast, instant claim 1 is drawn to an MHC class I-restricted epitope peptide derived from survivin, comprising the epitope peptide of SEQ ID NO: 5, wherein the epitope peptide is capable of eliciting IFN-γ producing cells in a PBL population of a patient having cancer disease wherein survivin is expressed.

As such the art reference is still a 102(b) art reference that constitutes a statutory bar that can not be overcome by a Katz-type declaration. The second cited Andersen reference is an evidentiary reference.

14. Claims 1, 21, 23, 24, 36 and 38-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Andersen *et al* (Cancer Res. 2001, 61: 5964-5968, IDS reference).

Andersen *et al* teach the peptide LMLGEFLKL (human servivin substitution analog peptide, SEQ ID NO: 5 of the instant claims). Andersen *et al* teach that HLA-A2/peptide complexes were multimerized, that the LMLGEFLKL peptide could be used to isolate and stimulate CTL that produce INF-γ, and that these CTL could lyse (*i.e.,* exhibit cytotoxicity against) the HLA-A2 positive breast cancer cell line MCF-7 and the HLA-A2-positive melanoma cell line FM3. Andersen *et al* also teach the survivin LTLGEFLKL nonamer peptide (see entire reference, especially results).

Claim 36 is included in this rejection because the peptides were used in solution when added to the ELISPOT wells, *i.e.,* were in a composition that was used for *ex vivo* detection or diagnosis of the presence in a cancer patient of survivin reactive T cells among PBL. In addition, the intended use of the composition comprising the peptide "for *ex vivo* or *in situ* diagnosis" recited in the said claims does not carry patentable weight *per se*, and the claims read on the active or essential ingredients of the composition.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's said arguments are of record on pages 20-22 of the amendment filed 12/12/08.

Applicant argues that the earliest priority filing (60/352,284) was filed on January 30, 2002 and includes disclosure of at least SEQ ID NO: 5, to which amended claim 1 in now directed. Applicant presents a table citing instant claim number and exemplary support in the said priority filing. Applicant further argues that both Andersen references were published less than one year prior to the filing of Applicant's provisional application 60/352,284, the references are not prior art under 35 USC 102(b). Applicant argues

that a declaration under 37 CFR 1.132 by Inventor Andersen (of record) with regard to these references has been previously submitted to the Office.

However, the instant claims do not have support in the parent provisional application 60/352,284 because ultimate base claim 1 is not drawn to a peptide consisting of SEQ ID NO: 5 (SEQ ID NO: 5 being disclosed in '284), and the limitations of claim 1 are not supported by the disclosure of '284.

Applicant cites p.3, Table 1, p. 11 at lines 5-18 and p. 12 at lines 15-35 of '284 for support for current claim 1.

p. 3 at Table 1 discloses a peptide consisting of SEQ ID NO: 5, p. 11 at lines 5-18 discloses ELISPOT assay for quantifying peptide epitope-specific IFN-g releasing effector cells, and use of Sur1M2 (SEQ ID NO: 5) in the assay, and p. 12 at lines 15-35 disclose survivin-reactive T cells in PBL from HLA-A2 positive breast cancer patients by ELISPOT assay.

In contrast, instant claim 1 is drawn to an MHC class I-restricted epitope peptide derived from survivin, comprising the epitope peptide of SEQ ID NO: 5, wherein the epitope peptide is capable of eliciting IFN-γ producing cells in a PBL population of a patient having cancer disease wherein survivin is expressed.

As such the art reference is still a 102(b) art reference that constitutes a statutory bar that can not be overcome by a Katz-type declaration.

15. Claims 1, 21, 23-25, 28, 33-35, 36, 38-40 and 50 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 02/072631 A2 (9/19/02).

WO 02/072631 A2 teaches a peptide with the sequence LMLGEFLKL, the sur1M2 peptide analog that binds to HLA-A2.1, which peptide sequence is identical to SEQ ID NO: 5 of the instant claims, and use of the peptide for detection of T cells specific for the complex formed by HLA-A2.1 and the said peptide. WO 02/072631 A2 further teaches complexes of this peptide with HLA-A2 and including in the form of a therapeutic composition (especially abstract, Example 1 at page 159, claims 1-42, and claim 82).

With regard to the inclusion of claims 25, 28, 33-36 and 50, the MHC/peptide complexes are a composition comprising the peptide. The instant claims do not recite wherein the peptide is isolated.

With regard to the limitation "vaccine" recited in instant claims 33-35 and 50, if the vaccine merely comprises a known composition, the term carries little weight absent evidence of structural difference.

With regard to the inclusion of claim 25 in this rejection, the claim recites "an immunogenic composition capable of eliciting an immune response against a cancer disease." Claim 50, also included in this rejection, recites "the immunogenic composition." Although the art reference does not teach either limitation, the art reference does teach that the pepide/MHC complexes are useful for therapy, and detection of T cells specific for the complexes. Therefore the claimed composition appears to be the same as the composition of the prior art absent a showing of differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show a distinction between the composition of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 1, 21, 23-25, 28, 33-36, 38-40 and 50 are rejected under 35 U.S.C. 103(a) as being obvious over Andersen *et al* (Cancer Res. 2001, 61: 5964-5968, IDS reference) in view of U.S. Patent No. 6,572,864 (of record).

Andersen *et al* teach the human servivin peptide LMLGEFLKL (substitution analog peptide, SEQ ID NO: 5 of the instant claims). Andersen *et al* teach that HLA-A2/peptide complexes were multimerized, that the LMLGEFLKL peptide could be used to isolate and stimulate CTL that produce INF-γ, and that these CTL could lyse (*i.e.,* exhibit cytotoxicity against) the HLA-A2 positive breast cancer cell line MCF-7 and the HLA-A2-positive melanoma cell line FM3. Andersen *et al* also teach the survivin LTLGEFLKL nonamer peptide. Andersen *et al* teach combining a survivin based immunotherapy with conventional cancer chemotherapy to ascertain if the combination may prove to be an effective modus operandi to fight cancer (see entire reference, especially results).

Andersen *et al* do not teach wherein the peptide is comprised in a pharmaceutical composition.

U.S. Patent No. 6,572,864 discloses formulating peptide epitopes or analogs thereof in a suitable diluent such as saline or water or adjuvants for use in a pharmaceutical composition.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have put the peptide taught by Andersen *et al* in a pharmaceutical composition as disclosed by U.S. Patent No. 6,572,864.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to test the peptide *in vivo* to ascertain treatment efficacy.

With regard to the limitation "vaccine" recited in instant claims 33-35 and 50, if the vaccine merely comprises a known composition, the term carries little weight absent evidence of structural difference.

With regard to the inclusion of claim 25 in this rejection, the claim recites "an immunogenic composition capable of eliciting an immune response against a cancer disease." Claim 50 also included in this rejection recites "the immunogenic composition." Although the primary art reference does not teach either limitation, the art reference does teach CTL response against this peptide in CLL patients using the ELISPOT assay. Therefore the claimed composition appears to be similar to the composition of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show an unobvious distinction between the composition of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

18. Claims 1, 21, 23-25, 28, 33-36, 38-40 and 50 are rejected under 35 U.S.C. 103(a) as being obvious over Andersen *et al* (Cancer Res. 2/2001, 61: 869-872, IDS reference) in view of U.S. Patent No. 6,572,864 (of record).

It is noted by the Examiner that the publication date listed on the Andersen *et al* (Cancer Res. 2/2001, 61: 869-872, IDS reference), *i.e.,* 2/2000, is a print error on the part of the publisher. The said reference is published in volume 61, publication date 2/2001.

Andersen *et al* teach the human survivin peptide with the sequence LMLGEFLKL (1 uM, substitution analog peptide), that corresponds to SEQ ID NO: 5 of the instant claims. Andersen *et al* further teach that this peptide has a *C50* (uM) value of 1 uM as determined in an assembly assay for peptide binding to HLA-A2.1 molecules. Andersen *et al* teach that a CLL cancer patient's IFN-γ producing PBL responded strongly against the analog peptide LMLGEFLKL at 35 per 10^4 cells in an ELISPOT assay. Andersen *et al* teach that survivin may serve as a widespread target for therapeutic CTL responses for anticancer immunotherapeutic strategies (see entire reference, especially Table 1 and Results).

U.S. Patent No. 6,572,864 discloses formulating peptide epitopes or analogs thereof in a suitable diluent such as saline or water or adjuvants for use in a pharmaceutical composition.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have put the peptide taught by Andersen *et al* in a pharmaceutical composition as disclosed by U.S. Patent No. 6,572,864.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to test the peptide *in vivo* to ascertain treatment efficacy.

With regard to the limitation "vaccine" recited in instant claims 33-35 and 50, if the vaccine merely comprises a known composition, the term carries little weight absent evidence of structural difference.

With regard to the inclusion of claim 25 in this rejection, the claim recites "an immunogenic composition capable of eliciting an immune response against a cancer disease." Claim 50 also included in this rejection recites "the immunogenic composition." Although the primary art reference does not teach either limitation, the art reference does teach CTL response against this peptide in CLL patients using the ELISPOT assay. Therefore the claimed composition appears to be similar to the composition of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show an unobvious distinction between the composition of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

19. Applicant's amendment filed 12/12/08 has overcome the prior rejection of record of claims 1, 17, 20-24, 36 and 38-40 under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 6,346,389.

20. Applicant's amendment filed 12/12/08 has overcome the prior rejection of record of claims 1, 17, 20-24, 36 and 38-40 under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,346,389.

21. Applicant's amendment filed 12/12/08 has overcome the prior art rejection of record of claims 1, 17, 20-25, 28 and 32-37 under 35 U.S.C. 103(a) as being obvious over WO 00/03693 A1 (IDS reference) in view of Rammensee *et al* (MHC Ligands and Peptide Motifs. Springer, Landes Bioscience, USA, pages 217-228 and 238-243, 1997, of record), Ruppert *et al* (Behring Inst. Mitt., No. 94, 48-60 (1994), Conway *et al* (Blood, 2/15/00, 95(4): 1435-1442) and U.S. Patent No. 6,572,864 (of record).

22. Applicant's amendment filed 12/12/08 has overcome the prior art rejection of record of claims 38-40 under 35 U.S.C. 103(a) as being obvious over WO 00/03693 A1 (IDS reference) in view of Rammensee *et al* (MHC Ligands and Peptide Motifs. Springer, Landes Bioscience, USA, pages 217-228 and 238-243, 1997, of record), Ruppert *et al* (Behring Inst. Mitt., No. 94, 48-60 (1994), Conway *et al* (Blood, 2/15/00, 95(4): 1435-

1442) and U.S. Patent No. 6,572,864 as applied to claims 1, 17, 20-25, 28 and 32-37 above, and further in view of WO 99/50637.

23. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

24. Claims 1, 21, 23-25, 28, 33-36, 38-40 and 50 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4-7, 14, 17-24, 26-34, 44 of copending Application No. 10/354,090 in view of Andersen *et al* (Cancer Res. 2001, 61: 5964-5968, IDS reference) or Andersen *et al* (Cancer Res. 2/2001, 61: 869-872, IDS reference) or WO 02/072631 A2.

This is a provisional obviousness-type double patenting rejection.

The claims (other than claim 7) of 10/354,090 differ from the instant claims in that they do not recite the sur1M2 peptide LMLGEFLKL that is SEQ ID NO: 5 of the instant claims, and claim 31 10/354,090 of differs in that it recites "kit."

The two Anderson *et al* references as well as WO 02/072631 A2, discussed supra, all teach the sur1M2 LMLGEFLKL peptide derived from survivin that binds to HLA-A2.1 and its use to stimulate T cells.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the sur1M2 peptide taught by the two Anderson *et al* references as well as WO 02/072631 A2 as the HLA-A2.1 class I-restricted peptide derived from survivin in the claims of 10/354,090.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because the references teach the usefulness of the sur1M2 peptide to stimulate T cells.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have placed the sur1M2 peptide in a kit as per the recitation in claim 31 of 10/354,090, for convenience of use, and particularly in light of the teachings of any one of the references that the peptide can be used to detect T cells.

25. Claims 1, 21, 23-25, 28, 33-36 and 50 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 6, 9, 11, 12, 14-1627-37 and 44 of copending Application No. 10/543,755. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are drawn to a peptide derived from survivin comprising the epitope peptide of SEQ ID NO: 5 (the Sur1M2 LMLGEFLKL peptide), while the claims of 10/543,755 are drawn to a composition comprising SEQ ID NO: 5 in combination with three other peptides derived from survivin.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

26. Claims 38-40 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 6, 9, 11, 12, 14-16, 27-37 and 44 of copending Application No. 10/543,755 in view of WO 02/072631 A2.

WO 02/072631 A2 teaches a peptide with the sequence LMLGEFLKL, the sur1M2 peptide analog that binds to HLA-A2.1, which peptide sequence is identical to SEQ ID NO: 5 of the instant claims, and use of the peptide for detection of T cells specific for the complex formed by HLA-A2.1 and the said peptide. WO 02/072631 A2 further teaches complexes of this peptide with HLA-A2 and including in the form of a therapeutic composition (especially abstract, Example 1 at page 159, claims 1-42, and claim 82).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have formulated the peptide in the claims of 10/543,755 as an MHC complex with HLA-A2.1 as per the teaching of WO 02/072631 A2.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because WO 02/072631 A2 teaches the usefulness of these complexes for detection and therapy.

27. No claim is allowed.

28. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Eileen B. O'Hara, can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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February 5, 2009

/G.R. Ewoldt/
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